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Association between epicardial fat thickness and cognitive function in elderly. A preliminary study

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Abstract

Background. Recent studies suggested that the visceral fat could exert a predictive role in the pathogenesis of dementia. The aims of the present study were to evaluate: i) possible differences between groups with different epicardial adipose tissue (EAT) thickness on the included variables; ii) the possible predictive role of the EAT levels on cognitive functioning.

Methods. 65 community-dwelling subjects were enrolled and divided into two groups: EAT < 7 mm (n = 36); EAT > 7 mm (n = 29). The metabolic profile was assessed through the evaluation of the biochemical parameters whereas the EAT thickness was measured through the transthoracic echocardiography. The Mini Mental State Examination (MMSE) was also administered.

Results. The two EAT groups reported several significant differences, included on the MMSE scores. The multiple linear regression analysis showed that the EAT thickness levels and the hypertension had a predictive effect on the MMSE scores.

Conclusions. These preliminary findings support the association between EAT thickness levels and cognitive impairment.

Key words

- epicardial fat thickness
- cardiometabolic risk
- cognitive impairment
- visceral fat

INTRODUCTION

A multifactorial pathogenesis is assumed for dementia. Indeed, while cardiovascular and metabolic factors are acknowledged as being relevant in the pathogenesis of "vascular dementia", growing interest has been reported about the potential role of these factors in degenerative dementia as well. The importance of such factors is still controversial and research on this matter is being carried out. Over the past years, the role of adipose tissue as a possible risk factor has stirred great interest. By releasing different mediators, adipose tissue exerts a negative action on different organs and systems, including the cardiovascular [1] and nervous systems [2]. Adipose tissue can be classified according to its position in subcutaneous or visceral. In the latter type, epicardial adipose tissue (EAT) presents a unique location, being close or in contact with the heart and the coronary arteries. EAT is an energy source regulating the homeostasis of fatty acids for coronary circulation. Moreover, it produces a "cocktail" of cytokines (IL-6, TNF-α), adipokine (adiponectine), microRNA and other cell mediators (leptin, angiotensinogen, resistin), playing a fundamental role in the paracrine regulation of vascular tone, in muscular smooth vascular cell proliferation and migration, and in susceptibility to atherosclerosis [2].

Over time, more and more convincing evidence has led researchers to believe that this tissue could be involved, through a pathogenic pattern of "initial local inflammation", in different cardiometabolic phenomena such as insulin resistance and atherosclerosis. Thus, it can be concluded that EAT represents an authentic cardiovascular risk factor [3]. Nevertheless, the role of EAT in the development of cognitive impairments is still to be clarified. More specifically, can EAT thickness be considered a reliable or predictive indicator for cognitive impairment?

The primary aim of this study is to evaluate possible differences in both cognitive function and several vas-

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cular risk factors (e.g. hypertension, diabetes, metabolic parameters) in groups with different levels of EAT thickness.

Furthermore, a secondary aim of the study is to evaluate the possible predictive role of both the EAT levels and the vascular risk factors on the cognitive functioning.

MATERIALS AND METHODS

65 community-dwelling Caucasian subjects with a mean age of 72.1 years (standard deviation = 8.9; 31 males) followed by our Department for the evaluation of the functional status participated in this study. Exclusion criteria were: infectious diseases, thoracic trauma, surgical procedures in the last 90 days, alcohol or drug addiction, psychiatric disorders, depression, hypo- or hyperthyroidism, anemia by any cause, heart failure, or condition of being chronically ill and treatment with chemotherapeutic or hormonal agents. All procedures performed in this study which involved human participants were in accordance with our institutional research committee (15th of November 2017) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

The same day of the enrollment in the study each patient underwent a clinical interview, a physical examination, an anthropometric assessment and the venous blood sampling. Waist circumference (WC) was measured at the level of iliac crest in standing patients. After an overnight fast, standard laboratory techniques were used to determine the plasma total cholesterol (TC), high-density lipoprotein cholesterol (HDLc), triglycerides (TG) and fasting blood glucose (FBG).

Transthoracic two-dimensional (2D) guided M-mode echocardiography was performed in each subject using a Philips iE-33 machine (ultrasound device iE33 by Philips Ultrasound Inc., USA). Epicardial fat was recognized as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium at end-systole in three cardiac cycles. We measured EAT thickness on the free wall of the right ventricle from both parasternal long- and short-axis views. The maximum values at any site were measured, and the average value was considered. Different cut-off points of epicardial fat thickness for cardiometabolic risk prediction have been proposed [3]. Considering the heterogeneity of our sample in terms of cardiovascular risk factors, a threshold value of 7 mm thickness was fixed, in line with Natale et al. that set the normal upper limit to 7 mm [3, 4]. The clinical cut-off for EAT thickness values (= 7) was used in order to divide the sample in two groups: *Increased EAT thickness level* (n = 29, mean age = 73.9; SD = 8.3, 17 M; EAT mean values = 7.9; = 1.1) and *Normal EAT thickness level* (n = 36, mean age = 70.6; SD = 9.3, 14 M; EAT mean values = 5.6; = .82).

The cognitive function was assessed through the Mini Mental State Examination (MMSE) which maximum score is 30. A score below 27 is indicative of an increased risk of cognitive dysfunctions and dementia [5].

Hypertension was defined as a systolic arterial pressure (SBP) > 140 mmHg and a diastolic arterial pressure (DBP) > 90 mmHg or as reporting an history of use of antihypertensive medication, according to the WHO guidelines. Diabetes was defined as the pres-

Table 1
Differences between groups with normal and increased levels of epicardial adipose tissue (EAT) thickness

Parameters (n = 65) Epicardial adipose tissue thickness						
	< 7 mm (36)		> 7 mm (29)		f	p
	M	*SD*	*M*	*SD*		
Age	70.61	9.3	73.93	8.3	2289	0.13 (ns)
FBG	94.89	13.1	107.10	12.1	14983	0.001**
WC	89.17	11.0	100.15	14.3	12203	0.001**
HDLc	57.28	9.74	49.14	17.2	5790	0.02*
TG	114.98	23.8	138.90	45.33	7479	0.008**
MMSE	28.31	1.06	24.67	1.35	16320	0.001**
	n	*%*	*n*	*%*	χ^2	*p*
Gender						
Male	14	38.9	17	58.6	2507	0.09 (ns)
Female	22	61.1	12	41.4		
Hypertension						
No	11	30.6	0	0	10666	0.001**
Yes	25	69.4	29	100		
Diabetes						
No	32	88.9	15	51.7	11079	0.001**
Yes	4	11.1	14	48.3		
MetS						
No	34	94.4	2	6.9	49820	0.001**
Yes	2	5.6	27	93.1		

*p < 0.05; **p <0.01. FBG: fasting blood glucose; WC: waist circumference; HDLc: high-density lipoprotein cholesterol; TG: triglycerides; MMSE: Mini Mental State Examination; MetS: Metabolic syndrome.

Table 2
Regression model reporting the predictive effect on Mini Mental State Examination scores of the variables included

Variables	Beta	95% CI		t	p
EAT	-0.494	-1.110	-0.344	-3.800	0.001**
FBG	-0.135	-0.058	0.016	-1.130	0.263
WC	-0.018	-0.039	0.034	-0.156	0.877
HDLc	0.051	-0.029	0.045	0.432	0.668
TG	-0.176	-0.023	0.002	-1.658	0.103
Gender	-0.078	-1.276	0.599	-0.723	0.473
Hypertension	-0.213	-2.398	-0.059	-2.104	0.040*
Diabetes	0.029	-0.999	1.276	0.244	0.808
Age	-0.187	-0.093	0.002	-1.901	0.063

*p < 0.05 **p < 0.01. EAT: epicardial adipose tissue; FBG: fasting blood glucose; WC: waist circumference; HDLc: high-density lipoprotein cholesterol; TG: triglycerides.

ence of the fasting plasma glucose levels of 126 mg/dl (7 mmol/ l) or the presence of non-fasting blood glucose values equal to or greater than 200 mg/dl (11.1 mmol/l) or a history of diabetes treatment [6]. Impaired fasting glucose (IFG) was defined by FBG concentrations within the range 100-125 mg/dL [7]. Metabolic syndrome was diagnosed, according to National Cholesterol Education Program (NCEP) ATP III 2001 criteria [8], by the presence of three or more of the following features: WC ≥ 88 cm in women and ≥ 102 cm in men; HDLc < 50 mg/dL in women and < 40 mg/dL in men; FBG ≥ 100 mg/dL and/or antidiabetic treatment; fasting triglycerides ≥ 150 mg/dL; SBP ≥ 130 mmHg and/or DBP ≥ 90 mmHg and/or antihypertensive treatment.

All statistical analyses were performed using the Statistical Package for the Social Science (SPSS) version 24 for Windows. Data are presented as means and for continuous variables and as frequencies for discrete variables. One-way analysis of variance (ANOVA) was performed to investigate possible differences between groups in continuous variables while the Chi-square test ($\chi 2$) was used to explore differences between groups in discrete variables. A linear multiple regression model was performed in order to verify the predictive role of EAT, FBG, WC, HDLc, TG, MMSE, gender (0 = female; 1 = male), hypertension (0 = no; 1 = yes) and diabetes (0 = no; 1 = yes) on the MMSE scores. All the independent variables were entered simultaneously. Regression coefficients along with their 95% confidence interval (CI) were reported. A p value below .05 was considered statistically significant.

RESULTS

Data analysis showed that the two groups were homogenous for the variables age and gender, whereas significant differences emerged in all the other variables examined *(Table 1)*. More specifically the group with EAT > 7 mm showed higher levels of FBG, WC and TG and lower levels of HDLc and MMSE compared to the group with EAT < 7 mm. Furthermore, the group with EAT > 7 mm reported a significantly higher frequency of patients suffering from hypertension, diabetes and metabolic syndrome compared to the group with EAT < 7 mm.

The multiple linear regression analysis revealed the absence of collinearity problems (tolerance index>.50; VIF< 2). The model explains the 55% of the MMSE scores (R^2=.55; adjusted R^2=.48). The independent variables who showed a predictive effect on the MMSE scores were: EAT (beta = -.49; 95% CI = -1,110 – -.344; p <.001), and hypertension (beta = -.21; 95% CI = -2.398 – -.59; p = .04) *(Table 2)*. The variable MetS was not included in the regression model because the diagnosis of MetS depends on other variables which were included in the analysis.

DISCUSSION

In accordance with the findings of other authors [9], a connection between increased EAT thickness and MetS and its components was reported. EAT thickness enables a more reliable evaluation of visceral fat than WC. Furthermore, in order to calculate visceral fat, EAT is measurable with good sensitivity and specificity by means of ultrasound techniques (lower costs), whereas other techniques are inevitably less manageable and very expensive, such as magnetic resonance (MR) or dual-energy X-ray absorptiometry, DXA [10].

Although vascular risk factors including hypertension, diabetes and dyslipidaemia have been implicated in the risk of cognitive dysfunction [2], only in Mazzoccoli *et al*. an association between epicardial fat thickness and cognitive impairment in the elderly was found [11]. In our study the negative correlation between the EAT thickness and the MMSE was confirmed. The way in which such an interesting correlation is obtained, at least from an ethio-pathogenic point of view, is still to be clarified and investigated. Visceral fat, including EAT, could have an injurious effect on cognitive abilities because of the intermediation of several cytokine and non-cytokine molecules it produces. This is well described in cardiovasculpathic patients [2] but we still lack clinical studies with patients suffering from Mild Cognitive Impairment (MCI) or dementia. There are, nonetheless, known to be differences among patients with cognitive decline, about prognostic outcomes in relation to inflammatory status. In this light, the EAT would play a dual role as a pathogenetic factor as well as a potentially reversible risk factor. Moreover, several studies show a close correlation between EAT and cardiac function, regulated by the autonomous nervous system, with a reduction of the para-sympathetic activity and significant consequences in terms of arrhythmia and, indirectly, brain activity [12]. In this perspective, associating epicardial fat and sympathetic nervous system by utilizing an accurate and easily reproduced method such as the assessment of heart rate variability (HRV), could represent a further item to explore cognitive decline and frailty [13]. Finally, there are genetic factors implied in the regulation of epicardial fat thickness and these factors are also correlated with insulin resistance, forming a sort of model that includes dementia- inducing diseases such as Alzheimer's, as well as metabolic pathologies like diabetes [14]. Familiarity with these genes and understanding of their function could contribute, in turn, to better understanding the role played by EAT in both pathologies, as well as clarifying the mechanisms through which it performs its negative action [15].

The results of this study need to be interpreted in the light of some limitations. Firstly, we did not use the most accurate tools for the evaluation of visceral fat (e.g. whole-body magnetic resonance imaging). Secondly, the relatively limited sample size. Thirdly, our results suffer from a lack of knowledge about the inflammatory status of the patients.

CONCLUSIONS

The results of our study highlight that EAT thickness, measured by transthoracic echocardiography, is inversely related to cognitive function. Based on our study, the transthoracic echocardiography proved to be simple and affordable. For this reason, it is realistic to suggest its application among elderly people whose physical changes can play an important role in determining biases in the anthropometric parameters routinely used.

Author contributions

Verrusio W, Magro VM and Renzi A were the primary researchers and wrote the manuscript. Andreozzi P and Musumeci M provided research and editing assistance to the manuscript. Andreozzi P and Cacciafesta M contributed to overall article design, data collection as well as revising and approving the manuscript.

Conflict of interest statement

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